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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/675,927	09/29/2003	Payman Amiri	18773.004	2378

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EXAMINER	
KANTAMNENI, SHOBHA	
ART UNIT	PAPER NUMBER
1627	

MAIL DATE	DELIVERY MODE
01/03/2012	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/675,927	AMIRI ET AL.	
	Examiner	Art Unit	
	SHOBHA KANTAMNENI	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *75,76,78,80,82,83,89,93-95,98,100-103 and 108-118* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☒ Claim(s) *NONE* is/are allowed.

7)☒ Claim(s) *75,76,78,80,82,83,89,93-95,98,100-103,108-118* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 10/06/2011, wherein claims 75, 78, 82, 89, 98, 100, 101, 113, 114 have been amended, and new claims 115-118 have been added. Applicant's amendment also canceled claims 88, 91, 92, 96, 97, and 99.

Applicant's amendment overcomes the rejection of Claims 75-76, 78, 80, 82, 83, 88-89, 91-103, 108-114 under second paragraph of 35 U.S.C. 112.

The rejection of Claims 75-76, 78, 80, 82-83, 89, 93-95, 98, 100-103, 108-118 under 35 U.S.C. 112, first paragraph is MAINTAINED. See under response to arguments.

The rejection of Claims 75, 76, 78, 80, 82, 83, 88-89, 91-106, and 108-112 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 43-45 of U.S. Application No. 12/315,779, in view of instant specification is herein withdrawn. Note: Applicant has filed a terminal disclaimer.

The rejection of Claims 75, 76, 78, 80, 82, 83, 88-89, 91-106, and 108-112 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 7732465, in view of instant specification is herein withdrawn. Note: Applicant has filed a terminal disclaimer.

Claims 75, 76, 78, 80, 82, 83, 89, 93-95, 98, 100-103, 108-118 are pending, and examined herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 116-118 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 116 recites the limitation "A1 as pyridyl, pyrimidinyl, indolyl, isoxazolyl, indazolyl, imidazolyl, benzimidazolyl, napthyl, 9H-fluoren-1-yl, or furanyl" in the claim. There is insufficient antecedent basis for this limitation in the claim because A1 is a monocyclic cabocylic aryl group in claims 75, 76, 78, 80, 82, or 83.

Claim 116 recites the limitation "R1 is taken together with R2 to form substituted thiazolyl, oxadiazolyl, thiophenyl, furanyl, benzothiazolyl" in the claim. There is insufficient antecedent basis for this limitation in the claim because R1 is taken together with R2 to form a substituted C3-14 heteroaryl group, wherein the C3-14 heteroaryl group contains only carbon and nitrogen atoms as ring atoms in the claims 75, 76, 78, 80, 82, or 83.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 75-76, 78, 80, 82-83, 89, 93-95, 98, 100-103, 108-118 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for a method of inhibiting Raf kinase activity in a human or animal subject suffering from a

Ras/mitogen-activated protein kinase signal pathway-mediated cancer disorder selected from the group consisting of melanoma, breast cancer, prostate cancer, lung cancer, pancreatic cancer, thyroid cancer, bladder cancer, colon cancer, liver cancer, myeloid leukemia, and villous colon adenoma in a human or animal subject, comprising administering to the human or animal subject a composition comprising an amount of a specific compound represented by formula (II), does not reasonably provide enablement for inhibiting Raf kinase activity in a human or animal subject comprising administering a composition comprising **any compound/all compounds** represented by formula (II). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without **undue experimentation**. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1). The Nature of the Invention:

All of the rejected claims are drawn to an invention which pertains to a method of inhibiting Raf kinase activity in a human or animal subject comprising administering a composition comprising compound represented by formula (II).

(2). Breadth of the Claims:

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass method of inhibiting Raf kinase activity in a human or animal subject comprising administering a composition comprising any compound encompassed by the formula illustrated by the broad structure of formula (II).

What's more, the scope of the compounds claimed to be useful for the treatment method is extremely broad.

(3). Guidance of the Specification / (4). Working Examples:

Applicant provides in the specification on pages 307-309 *in vitro* assay protocol, Raf Screening in general. The specification merely recites on page 309 "Using the procedures of Examples 1401 or 1402, the compounds of Examples 1-1094 were shown to have a raf kinase inhibitory activity at an IC_{50} of less than 5 μM", out of Examples 1-1094, none of the compounds have for example A1 = (1,4'-bipiperidin-1'-ylcarbonyl)phenyl, R1, R2 taken together form pyrrole ring, tetrazole ring, or other heterocyclic rings containing more than 3 nitrogen atoms in the ring, as in instant claims. In instant claims 75, 78, 82 etc. A1 is substituted monocyclic carbocyclic aryl i.e aryl, can be substituted with cyclohexyl, heterocyclylphenyl which can include thousands of compounds with heteroatoms such as O, S, N, and different ring size etc.

as in page 16 of instant specification as in instant formula (II) as instant claims, 75, 78, 82 etc. There is no specific data i.e raf kinase inhibitory activity data, provided for any compounds of formula (II) as in instant claims 75, 78, 82, wherein A1 = (1,4'-bipiperidin-1'-ylcarbonyl)phenyl, A2 = pyridine, R1, R2 taken together form pyrrole ring, tetrazole ring, or other heterocyclic rings containing more than 3 nitrogen atoms in the ring, as in instant claims.

There are no working examples for the method of inhibiting Raf kinase activity in a human or animal comprising administering any compounds of Formula (II).

(5). State of the Art: / (6). Predictability of the Art:

While the state of the art is relatively high with regard to a method of inhibiting Raf kinase activity in human or animal comprising administering specific compounds, the state of the art with regard to a method of inhibiting Raf kinase activity comprising administering any compounds encompassed by formula (II) is underdeveloped.

It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839 (1970). In the instant case, as discussed above, there is a vast number of compounds encompassed by the claims, the specification merely recites that the compounds of Examples 1-1094 were shown to have a raf kinase inhibitory activity at an IC_{50} of less than 5 μM, out of Examples 1-1094. There is no specific data i.e raf kinase inhibitory activity data, provided for compounds of formula (II) when A2 is pyridyl, R1, R2 taken together form any or all C3-14 heteroaryl rings where the ring is for example triazole,

benzotriazole, pyrrole, purine etc. and A1 is any carbocylic aryl ring such as tetralinyl etc.as in instant claims.

It is pointed out that the compounds represented by formula (II) have wide variety of different functional groups, and will have different properties, e.g., physical, chemical, physiological effects and functions, since given the fact that any significant structural variation to a compound would be reasonably expected to alter its properties. For example, in instant formula (II) as in instant claims 75, 78, 82, 115-118, a compound with A1 = benzene, A2 = pyridine, R1, R2 taken together form tetrazole ring in formula (II) will have different physical, chemical, physiological effects and functions such as binding abilities, solubilities than a compound with A2 = pyridyl, A1 = (1,4'-bipiperidin-1'-ylcarbonyl)phenyl, R1, R2 form a purine ring, and thus will have different Raf kinase inhibitory activity. Also, in formula (II), A1 in instant claims 75, 78, 82 etc. is substituted monocyclic carbocyclic aryl i.e aryl, can be substituted with cyclohexyl, furanyl etc. which can include thousands of compounds with heteroatoms such as O, S, N, and different ring size. Furthermore, there is no evidence that the compounds actually inhibit Raf kinase activity in a human or animal. Moreover, one of skill in the art would recognize that it is highly unpredictable in regard to therapeutical effects, side effects, and especially serious toxicity that may be generated by drug-drug interactions when and/or after administering to a host (e.g., a human) any compound represented by formula II, and other anticancer agents. See "Goodman & Gilman's The Pharmacological Basis of Therapeutics" regarding possible drug-drug interactions (9th ed., 1996), page 51 in particular. Goodman & Gilman teaches that "The frequency of

significant beneficial or adverse drug interactions is unknown" (see the bottom of the left column of page 51) and that "Recognition of beneficial effects and recognition of and prevention of adverse drug interactions require a thorough knowledge of the intended and possible effects of drugs that are prescribed" and that "The most important adverse drug-drug interactions occur with drugs that have serious toxicity and a low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences" (see the right of page 51) (emphasis added). Thus, the compounds of formula (II) of the instant invention have different functional groups and result in different biological properties such as drug-drug interactions, formation of metabolites with different toxicities etc. Thus, the instant claimed invention as discussed above is **highly unpredictable**.

Moreover, the standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court of Mineral Separation v. Hyde, 242 U.S. 262, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied.

(7). The Quantity of Experimentation Necessary:

In order to practice the claimed invention, one of skill in the art would have to first envision a compound, a dosage for each compound, an appropriate pharmaceutical carrier, the duration of treatment, route of treatment, etc. and, in the case of human treatment, an appropriate animal model system for one of the claimed compounds. One would then need to test the compound in the model system to determine whether or not

the compound is effective for inhibiting Raf kinase acitivity, and determine whether or not the compound is effective in inhibiting Raf kinase acitivity in a human or animal subject suffering from a Ras/mitogen-activated protein kinase signal pathway-mediated cancer disorder selected from the group consisting of melanoma, breast cancer, prostate cancer, lung cancer, pancreatic cancer, thyroid cancer, bladder cancer, colon cancer, liver cancer, myeloid leukemia, and villous colon adenoma. One would then also need to test the compound in the model system for side effects and toxicity at the site of pharmacological action and the therapeutic index of the drug. Thus a person of skill in the art would have to engage in **undue experimentation** to test these compounds encompassed in the instant claims and their combination with other drugs to be administered to a host employed in the claimed methods of the particular treatments herein, with no assurance of success. If unsuccessful, one of skill in the art would have to then either envision a modification of the first pharmaceutical compound, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system, and test the system again. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention to inhibit Raf kinase activity in a human or animal subject by administration a composition comprising one of the compounds represented by formulas (II).

Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, the instant specification, does not enable the skilled artisan to make and use the claimed invention commensurate in scope with these claims.

Response to Applicant's Arguments:

Applicant's arguments have been considered, but not found persuasive. The specification merely recites on page 309 "Using the procedures of Examples 1401 or 1402, the compounds of Examples 1-1094 were shown to have a raf kinase inhibitory activity at an IC_{50} of less than 5 μM" It is pointed out that of Examples 1-1094, none of the compounds have for example A1 = (1,4'-bipiperidin-1'-ylcarbonyl)phenyl, R1, R2 taken together form tetrazole ring, or other heterocyclic rings containing more than 3 nitrogen atoms in the ring, as in instant claims. In instant claims 75, 78, 82 etc. A1 is substituted monocyclic carbocyclic aryl i.e aryl, can be substituted with cyclohexyl, heterocyclylphenyl which can include thousands of compounds with heteroatoms such as O, S, N, and different ring size etc. as in page 16 of instant specification as in instant formula (II) as instant claims, 75, 78, 82 etc. There is no specific data i.e raf kinase inhibitory activity data, provided for any compounds of formula (II) as in instant claims 75, 78, 82, 115-118, wherein A1 = (1,4'-bipiperidin-1'-ylcarbonyl)phenyl, A2 = pyridine, R1, R2 taken together form pyrrole ring, tetrazole ring, or other heterocyclic rings containing more than 3 nitrogen atoms in the ring, as in instant claims. It is further pointed out that the compounds represented by formula (II) have different functional groups, and will have different properties, e.g., physical, chemical, physiological effects and functions, since given the fact that any significant structural variation to a compound would be reasonably expected to alter its properties. For example, in instant formula (II)

as in instant claims 75, 78, 82, 115-118, a compound with A1 = benzene, A2 = pyridine, R1, R2 taken together form tetrazole ring in formula (II) will have different physical, chemical, physiological effects and functions such as binding abilities, solubilities than a compound with A2 = pyridyl, A1 = (1,4'-bipiperidin-1'-ylcarbonyl)phenyl, R1, R2 form a purine ring, and thus will have different Raf kinase inhibitory activity. Also, in formula (II), A1 in instant claims 75, 78, 82 etc. is substituted monocyclic carbocyclic aryl i.e aryl, can be substituted with cyclohexyl, furanyl etc. which can include thousands of compounds with heteroatoms such as O, S, N, and different ring size. In view of the structural divergence in the claims, one skilled in the art could not reasonably extrapolate the activities of some of the claimed compounds to the other structurally divergent compounds which are being used for their physiological activity, the scope of the claims must have a reasonable correlation to the scope of enablement provided by the specification. See *In re Surrey* 151 USPQ 724 regarding sufficiency of disclosure for a Markush group. No reasonable assurance has been made that the instant compounds as an entire class have the required activities needed to practice the invention. Thus, the instant claimed invention as discussed is **highly unpredictable** with respect to therapeutic effects employing the widely varying structural compounds.

Applicant argues that "that new claims 115-118 recite more specific substituent combinations." It is pointed out that for example, in instant formula (II) as in instant claims 115-118, a compound with A1 = benzene, A2 = pyridine, R1, R2 taken together form tetrazole ring in formula (II) will have different physical, chemical, physiological effects and functions such as binding abilities, solubilities than a compound with A2 =

pyridyl, A1 = (1,4'-bipiperidin-1'-ylcarbonyl)phenyl or hexylthiophenyl, R1, R2 form a purine ring, and thus will have different Raf kinase inhibitory activity. In view of the structural divergence in the claims, one skilled in the art could not reasonably extrapolate the activities of some of the claimed compounds to the other structurally divergent compounds which are being used for their physiological activity, the scope of the claims must have a reasonable correlation to the scope of enablement provided by the specification.

Further, the compounds tested demonstrated activity does not provide support that all or any of the compounds of the invention will inhibit Raf kinase activity in a human or animals, since instant compounds of formula (II) is broad, and include structurally different compounds. It is pointed out that the compound of Example 1, and the instant compounds of formula (II) wherein A1 is 4-amino(imino)methylphenyl and R1, R2 form tetrazole ring will have different structures and will have different properties such as binding abilities, solubilities, and Raf kinase activities. Thus, compound of Example 1 has been shown to be an inhibitor of Raf 1 kinase in human clinical trials does not provide support that all or any of the compounds of the invention will inhibit Raf kinase activity in a human or animals, since instant compounds of formula (II) are broad, and include structurally different compounds.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period, will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shobha Kantamneni whose telephone number is 571-272-2930. The examiner can normally be reached on Monday-Friday, 8am-4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, Ph.D can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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